



Arboviral Diseases

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UNCLASSIFIED



Lecture Objectives

- Increase knowledge of:
 - Arbovirology
 - Epidemiology of tropical viral disease threats
 - Select diseases clinical presentation
 - Key points related to prevention and treatment



Threat Assessment – ID Risk

Disease	2010 COCOM panel	ID-IDEAL
Malaria	1	2
Dengue	2	3
Diarrhea, bacterial	3	1
MDR wound pathogens	4	NA
Leishmaniasis	5	19
Q fever (Coxiella burnetti)	6	26
Norovirus / viral diarrhea	7	NA
Influenza	8	NA
Leptospirosis	10	7
Diarrhea, protozoal	11	11
TB	12	NA
CCHF	13	10
HIV	14	8
HFRS	15	17
Chikungunya	16	4
Meningococcal meningitis	17	20
Plague	18	27
Rickettsioses	19	18
Viral encephalitides	20	NA



What is a virus?

- Defined: A sub-cellular agent consisting of a **core of nucleic acid** surrounded by a **protein coat** that must use the **metabolic machinery of a living host to replicate** and produce more viral particles.
- Viruses are known to infect almost all organisms, including bacteria, fungi, plants, insects, and vertebrates.
- 20-300 nm in diameter; a “filterable” agent.



VIRUS STRUCTURE

Capsid

The capsid contains the virus' genetic material (DNA or RNA)

Viral envelope

The viral envelope is made from fatty lipid molecules taken from cells in the host

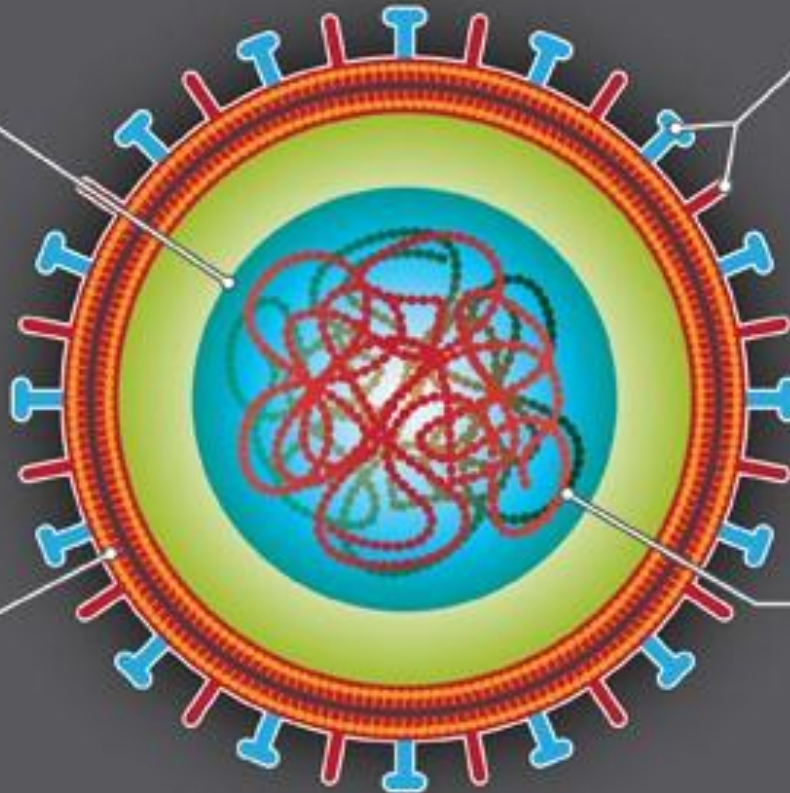
Surface proteins

These help the virus recognise and bind to cells in the host organism



Virus genetic material (DNA or RNA)

The virus' genetic material contains the instructions for making new copies of the virus



What is an arbovirus?

- Defined: Arthropod-borne viruses (arboviruses) are **transmitted biologically among vertebrate hosts by hematophagous (blood feeding) arthropod vectors** such as mosquitoes and other biting flies, and ticks.



Arboviral Transmission Dynamics



Virus

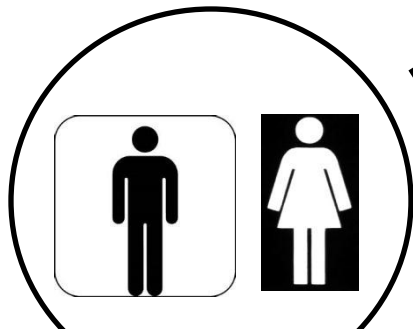


Vector

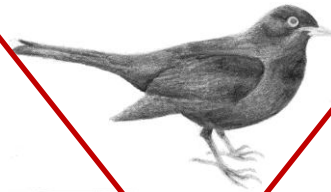
**Host
Reservoir**

Ecology

Ecology



Accidental Hosts



Transmission Cycle Example - WNV

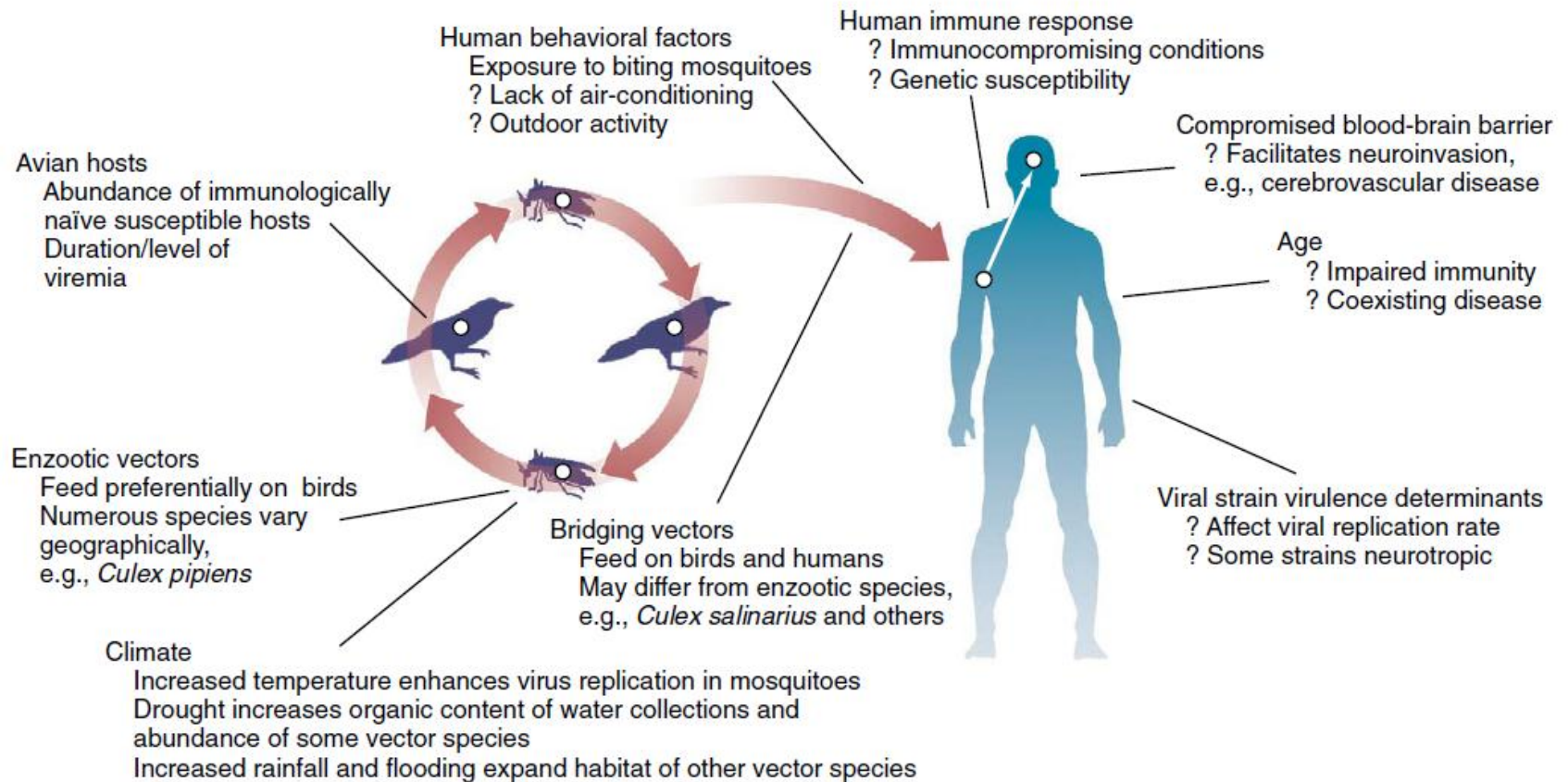


Figure 153-3 West Nile virus transmission cycle and examples of modifying climatologic, vertebrate, mosquito, and human factors on infection and illness.

Arboviruses

- Occur in nearly all parts of the world except the ice caps
- Over 500 distinct viruses, ~100 causing human infections
- Nearly all arboviruses included in 5 families:
 - Flaviviridae
 - Togaviridae
 - Bunyaviridae
 - Reoviridae
 - Rhabdoviridae



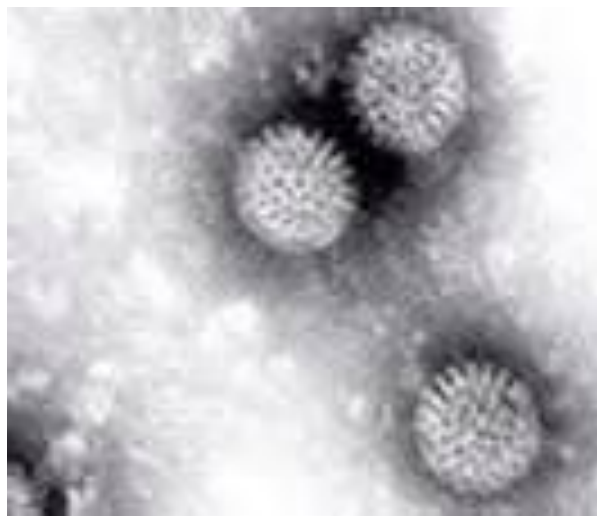
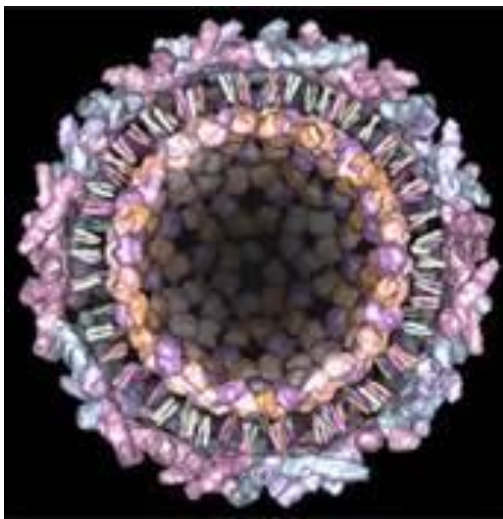
Question

- 50 yo Indian male presents with complaints of chronic pain and mild swelling in his fingers, bilaterally. He has no significant medical history except for a febrile illness he experienced 3 months ago following a trip to visit his family in southern India. He recalls the illness including fever, headache, fatigue, rash, and severe joint pain which lasted for ~9 days and spontaneously resolved without specific treatment. All symptoms resolved except for the joint pains which is why he presents today.
- What illness did the man experience following his trip 3 months ago?
 - A. Chikungunya
 - B. Dengue
 - C. Leptospirosis
 - D. Ross River virus
 - E. Enteric fever



Arboviruses

- Family Togaviridae
 - Genus Alphavirus (30 species, examples below)
 - Barmah Forest, **Chikungunya**, EEE, O'nyong-nyong, Ross River, Sinbis, VEE, WEE
 - Genus Rubivirus (1 species)
 - Rubella



Chikungunya

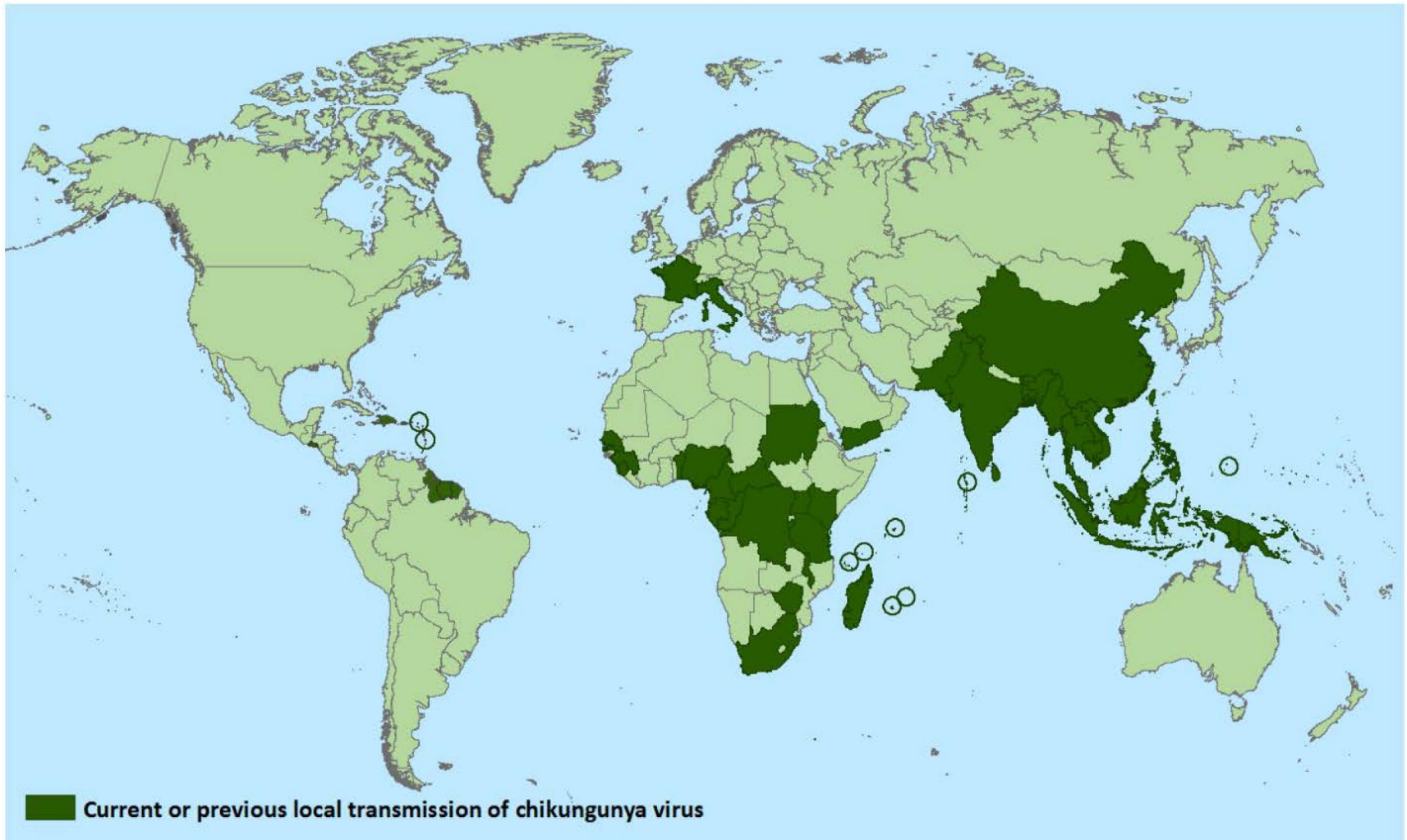
- Mosquito-transmitted *Alphavirus* (*Aedes* spp.)
- Historically, epidemic transmission patterns
 - Potential of sustained transmission in SE Asia?
- Recent outbreaks have infected hundreds of thousands
 - High clinical attack rates observed
 - Mortality increasingly observed
- Classic syndrome
 - Fever with polyarthrititis



— 100 —

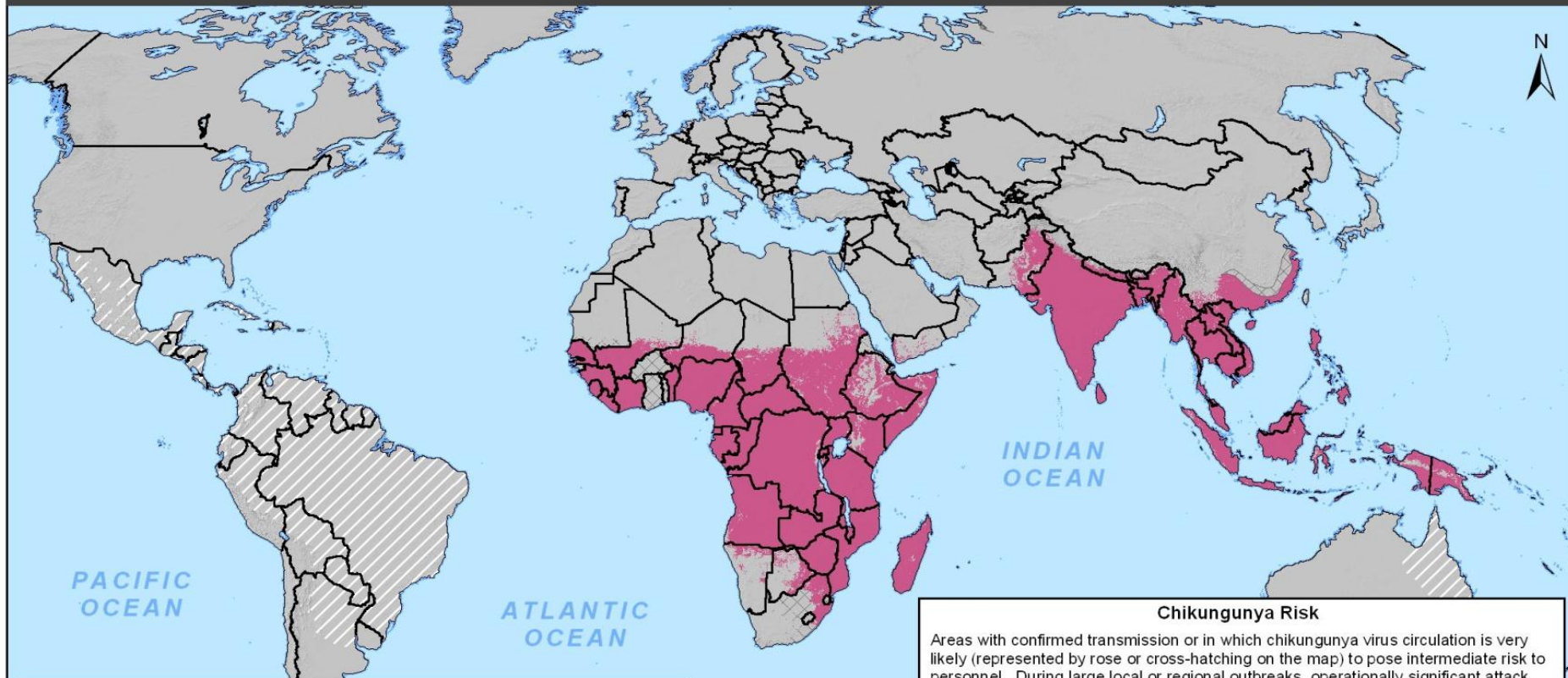


Countries and territories where chikungunya cases have been reported* (as of July 1, 2014)



*Does not include countries or territories where only imported cases have been documented. This map is updated weekly if there are new countries or territories that report local chikungunya virus transmission.

Worldwide: Chikungunya Risk to U.S. Forces



Note on Transmission and Risk

Because the vectors and epidemiology of dengue fever and chikungunya are very similar, the potential distribution of chikungunya parallels the known distribution of dengue fever. Chikungunya transmission and outbreaks are more intermittent and unpredictable than those seen in dengue. Intensity and duration of outbreaks are expected to be higher as population density increases. Outbreaks occur during the rainy season when day-biting mosquitoes are abundant and virus is introduced by an infectious person into a susceptible and densely populated area. The level of population immunity (known as herd immunity) is a major driver of chikungunya risk. In areas which have had recent outbreaks, herd immunity is high, making the risk of a subsequent outbreak very low for many years. As an increasing number of susceptible individuals are born into the population, the overall herd immunity declines. When population immunity is sufficiently low, explosive outbreaks often occur if/when the virus is introduced.

Chikungunya Risk

Areas with confirmed transmission or in which chikungunya virus circulation is very likely (represented by rose or cross-hatching on the map) to pose intermediate risk to personnel. During large local or regional outbreaks, operationally significant attack rates of 1-50% per month could occur among personnel exposed to mosquito bites.

- Chikungunya has been identified at the country level. Areas are assessed as environmentally suitable for chikungunya transmission.
- Chikungunya has not been reported but vectors are present, areas are environmentally suitable for transmission, the likelihood of introduction is high, and disease surveillance is limited (therefore transmission is likely to occur undetected).
- Currently no risk – in these areas mosquito vectors are present, chikungunya circulation has not been detected despite adequate surveillance and diagnostic capabilities; however, dengue transmission is known occur.
- No risk. Environmental conditions are unsuitable for transmission.

NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and U.S. government risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.

Clinical Manifestations

- Majority of infected people become symptomatic
- Incubation period usually 3–7 days (range 1–12 days)
- Acute onset of fever and polyarthralgia
- Joint symptoms usually symmetric
 - Hands and feet
 - Can be severe and debilitating
- Headache, myalgia, arthritis, conjunctivitis, nausea/vomiting, maculopapular rash
- Lymphopenia, thrombocytopenia, elevated creatinine, and elevated hepatic transaminases



Clinical Manifestations

Symptom or sign	Frequency range (% of symptomatic patients)
Fever	76–100
Polyarthralgias	71–100
Headache	17–74
Myalgias	46–72
Back pain	34–50
Nausea	50–69
Vomiting	4–59
Rash	28–77
Polyarthritis	12–32
Conjunctivitis	3–56

^aTable compiled from a number of different studies.^{8, 9, 12-17}

Pan American Health Organization
Preparedness and Response for Chikungunya Virus: Introduction in the Americas
Washington, D.C.: PAHO, © 2011



Clinical Manifestations - Rash



Chikungunya vs. Dengue

Clinical and laboratory features	Chikungunya virus infection	Dengue virus infection
Fever (>102°F or 39°C)	+++	++
Myalgias	+	++
Arthralgias	+++	+/-
Headache	++	++ ^b
Rash	++	+
Bleeding dyscrasias	+/-	++
Shock	-	+
Leukopenia	++	+++
Neutropenia	+	+++
Lymphopenia	+++	++
Elevated hematocrit	-	++
Thrombocytopenia	+	+++

^a Mean frequency of symptoms from studies where the two diseases were directly compared among patient seeking care; +++ = 70-100% of patients; ++ = 40-69%; + = 10-39%; +/- = <10%; - = 0%^{32, 33}

^b Often retroorbital

Table modified from Staples et al.³⁴

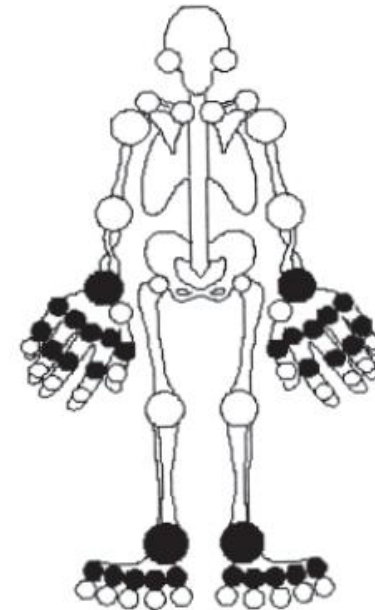


Figure 1. Affected joints (in black) in a patient with CHIKV polyarthritis presenting 6 weeks after onset of illness.

Chikungunya viral polyarthritis.

Raj J Carmona, Saeed Shaikh and Nader A Khalidi

J Rheumatol 2008;35;935-936

Chikungunya: A Potentially Emerging Epidemic?

Michelle M. Thiboutot^{1,2}, Senthil Kannan², Omkar U. Kawalekar², Devon J. Shedlock², Amir S. Khan³, Gopalsamy Sarangan⁴, Padma Srikanth⁴, David B. Weiner², Karupppiah Muthumani^{2*}

Table 1. Comparison of clinical features of Chikungunya and Dengue virus.

Clinical Features	Chikungunya Virus (CHIKV)	Dengue Virus (DENV)	Reference
1) Fever, asthenia	Common	Common	[6,8]
2) Myalgia	Possible	Very common	[6]
3) Polyarthrits	Very Common, edematous	None	[56]
4) Tenosynovitis	Yes	None	[57]
5) Leukopenia	None	Yes	[58]
6) Thrombocytopaenia	None	Yes	[59]
7) Rash	Days 1–4, important skin edema	Days 3–7	[6,35,58]
8) Retro-orbital pain	Rare	Common	[60]
9) Hypotension	Possible	Common, Days 5–7	[60,61]
10) Minor bleeding	Chronic polyarthrits up to 1 year	Common	[17,56]
11) Second stage	Possible; Tenosynovitis at M2–M3 Raynaud's syndrome at M2–M3	Fatigue up to 3 mo	[6,56,57,58,62,63]

doi:10.1371/journal.pntd.0000623.t001



Atypical Clinical Manifestations

System	Clinical manifestations
Neurological	Meningoencephalitis, encephalopathy, seizures, Guillain-Barré syndrome, cerebellar syndrome, paresis, palsies, neuropathy
Ocular	Optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis
Cardiovascular	Myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability
Dermatological	Photosensitive hyperpigmentation, intertriginous aphthous-like ulcers, vesiculobullous dermatosis
Renal	Nephritis, acute renal failure
Other	Bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypoadrenalism

Adapted from Rajapakse et al. ²⁰



Diagnosis

Figure 2. Viremia and immune response following Chikungunya virus infection.

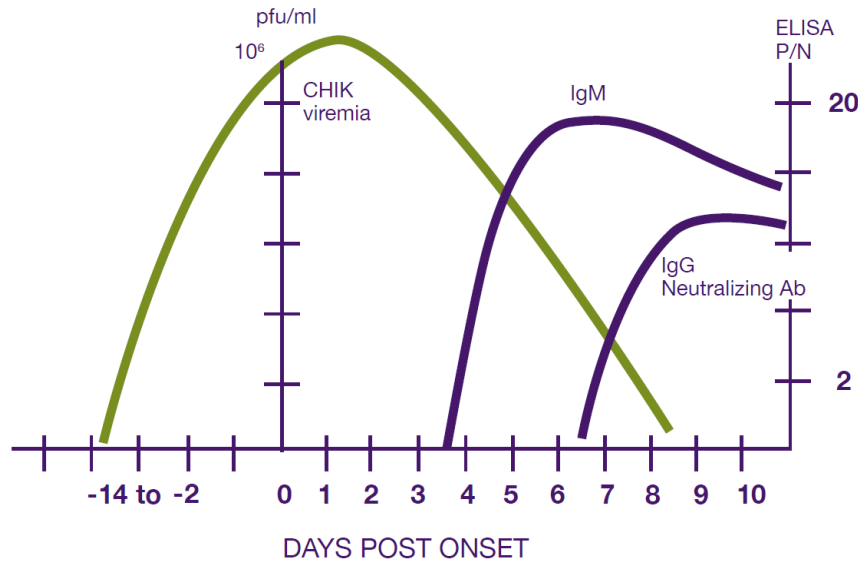


Table 6. Typical results of samples tested at various time points post-infection.

Days post illness onset	Virus testing	Antibody testing
Day 1-3	RT-PCR = Positive Isolation = Positive	IgM = Negative PRNT = Negative
Day 4-8	RT-PCR = Positive Isolation = Negative	IgM = Positive PRNT = Negative
>Day 8	RT-PCR = Negative Isolation = Negative	IgM = Positive PRNT = Positive

- Confirming a recent CHIKV infection:
 - Isolation of CHIKV, confirmatory identification (IFA, RTPCR, sequencing).
 - Detection of CHIKV RNA by real time RT-PCR.
 - Identification of a positive IgM result + acute symptoms, followed by the demonstration of CHIKV-specific antibody determined by PRNT with viruses in the SFV serogroup.
 - Seroconversion or a four-fold rise in PRNT, HI, or ELISA titers

Treatment

- No specific antiviral therapy; treatment is symptomatic
- Assess hemodynamic status and provide supportive care
- Evaluate for other serious conditions and treat appropriately
- Collect specimens for diagnostic testing
- Acetaminophen or paracetamol for initial fever and pain
- Consider using narcotics or NSAIDs
- If the patient may have dengue, do not use aspirin or other NSAIDs (e.g., ibuprofen, naproxen, toradol) until they have been afebrile ≥ 48 hours and have no warning signs for severe dengue
- Persistent joint pain may benefit from use of NSAIDs, corticosteroids, or physiotherapy



Outcomes

- Acute symptoms typically resolve within 7–10 days
- Complications
 - Uveitis, retinitis, myocarditis, hepatitis, nephritis, bullous skin lesions, hemorrhage, meningoencephalitis, myelitis, Guillain-Barré syndrome, and cranial nerve palsies
- Severe disease
 - Neonates exposed intrapartum, older adults (e.g., > 65 years), and persons with underlying medical conditions (e.g., hypertension, diabetes, or cardiovascular disease)
- Rheumatologic symptom relapse
 - polyarthralgia, polyarthritis, tenosynovitis
- Persistent joint pains for months to years possible



Persistent Chikungunya

Three clinical components, singly / in combination:

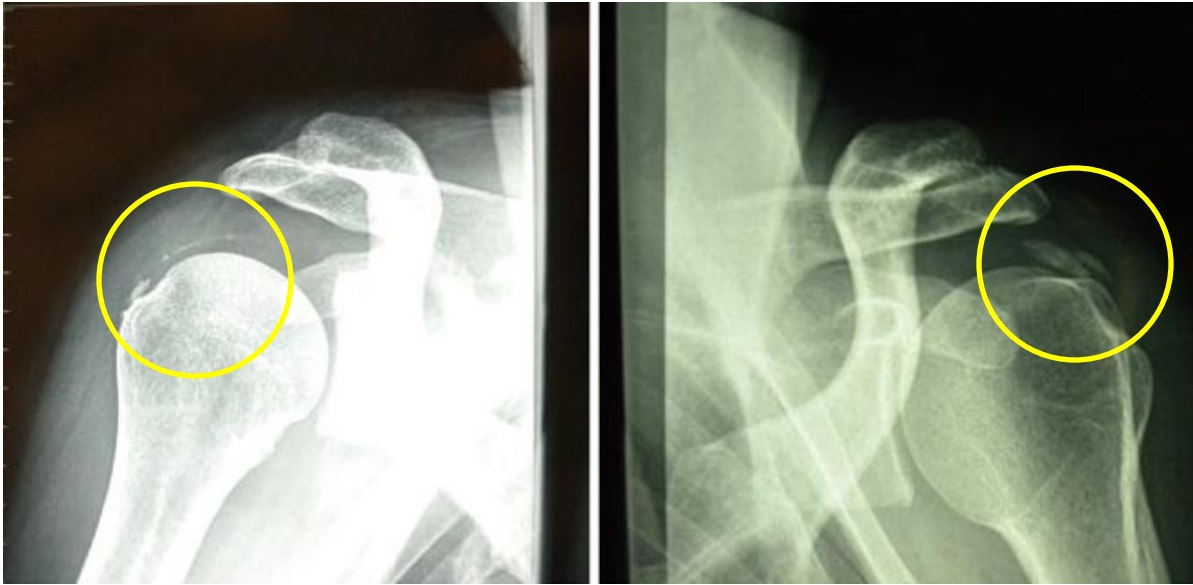
1. Distal polyarthritis / monoarthritis improved with NSAIDs.
2. Frequent tenosynovitides in the hands, wrists, or ankles, sometimes responsible for carpal or tarsal tunnel syndromes, highly sensitive to short-term systemic corticotherapy, and
3. Exacerbation of pain in previously injured joints and bones requiring painkillers.



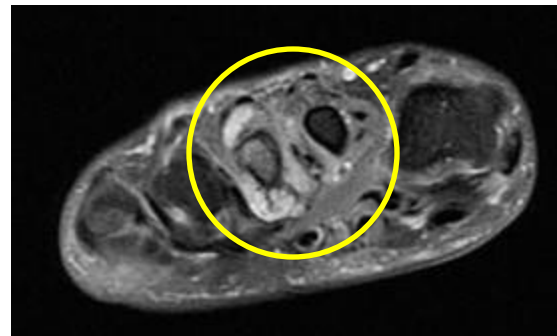
Persistent Chikungunya



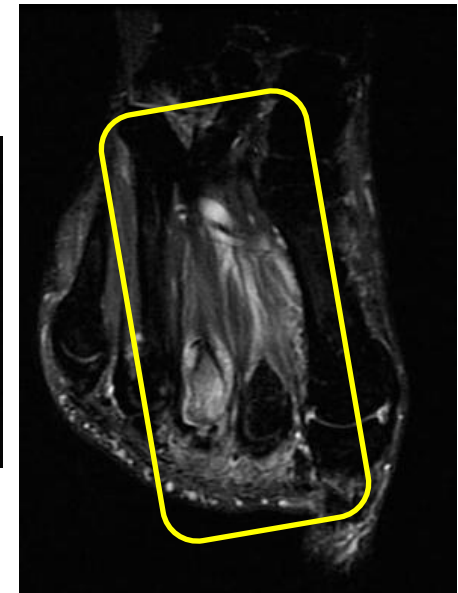
Persistent Chikungunya



Calcifications in shoulder tendon 18 months after infection



Inflammatory osteoarthritis, foot, 5 years after infection



Question

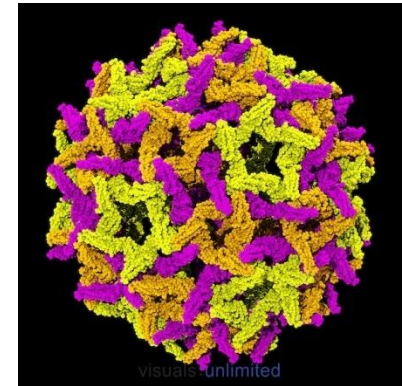
- A 67 yo male from presents with a five-day history of a febrile illness, headache, severe abdominal pain, anxiety, nausea and vomiting, dyspnea, jaundice, leukopenia, and thrombocytopenia. He lives in the eastern rain forest of Ecuador. He does not drink ETOH or use tobacco. He is up to date on all immunizations including yellow fever vaccine received 5 days prior to onset of symptoms. On admission, his BP was 110/70, HR of 72, a RR of 20, a temp. of 36°C, and O2 saturation rate of 74% on room air. Three hours after admission, he was transferred to an intensive care unit because of multiorgan system failure, oliguric renal failure. He experienced a cardiac arrhythmia and died.
- What is the most likely cause of the patient's demise?
 1. Severe dengue
 2. YF vaccine-associated neurologic disease (YEL-AND).
 3. YF vaccine-associated viscerotropic disease (YEL-AVD)
 4. Sylvatic YF

Case Report: Richard W. Douce *Am. J. Trop. Med. Hyg.*, 82(4), 2010, pp. 740–742



Arboviruses

- Family Flaviviridae
 - Genus Flavivirus (53 species, examples below)
 - Dengue, Japanese encephalitis, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever virus, Powassan, Rio Bravo, SLE, TBE, WNV, **Yellow fever**, Zika virus
 - Genus Hepacivirus (1 species)
 - Hepatitis C virus
 - Genus Pegivirus (2 species)
 - Pegivirus A, Pegivirus B
 - Genus Pestivirus (4 species)
 - Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus



Yellow Fever

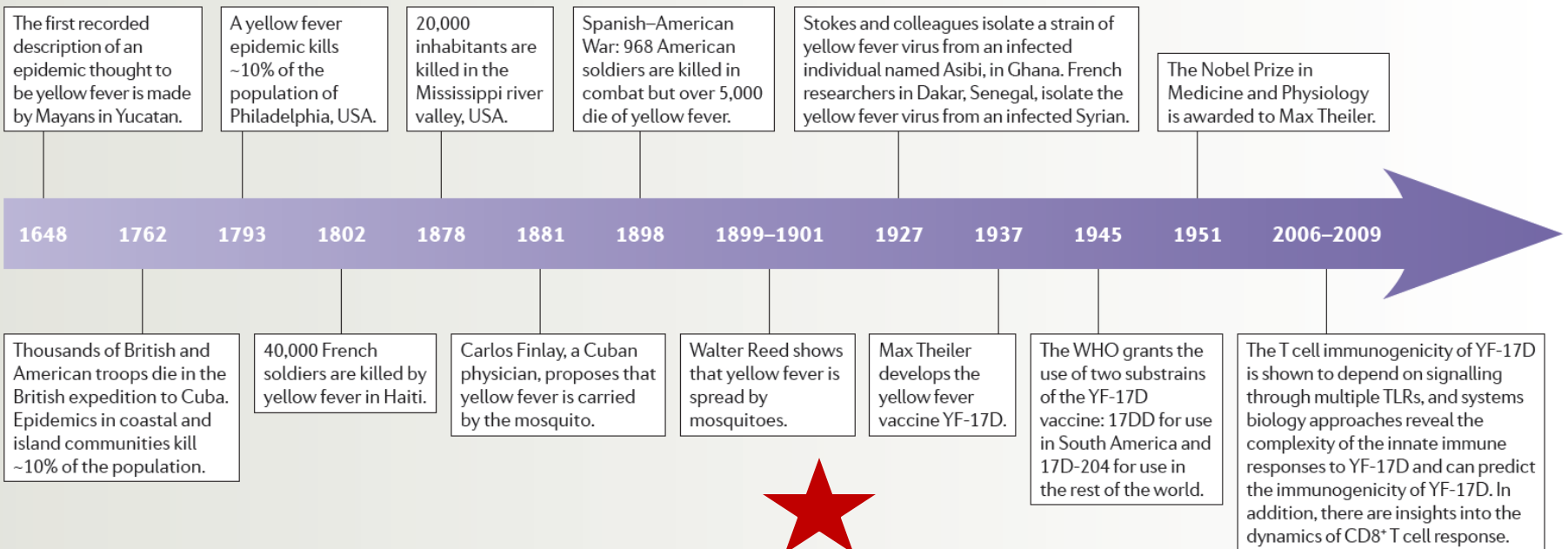
Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology

Bali Pulendran

NATURE REVIEWS | IMMUNOLOGY

VOLUME 9 | OCTOBER 2009 | 741

Timeline | Events in the development and understanding of the YF-17D vaccine



TLR, Toll-like receptor; WHO, World Health Organization.



Walter Reed Yellow Fever Commission



- Experiment summary
 - 14 non-fatal human challenge cases of YF produced
 - Transmission cycle revealed
 - Reed et al. publish results in JAMA, 1901
 - Army orders Gorgas to complete source reduction
 - In 90 days Havana is free of YF



Havana in 1900



Yellow Fever Virus

- Virus
 - Flavivirus (YF, JE, WNV, DENV)
 - 1 serotype
 - 5 genotypes within serotype
- Vector
 - Mosquito (*Aedes* spp.)
- Phylogenetic analyses
 - Evolved over 3000 yrs
 - YF virus originated in Africa
 - Divided into West and East African lineages
 - W. African lineage
 - Imported into S. America and New World

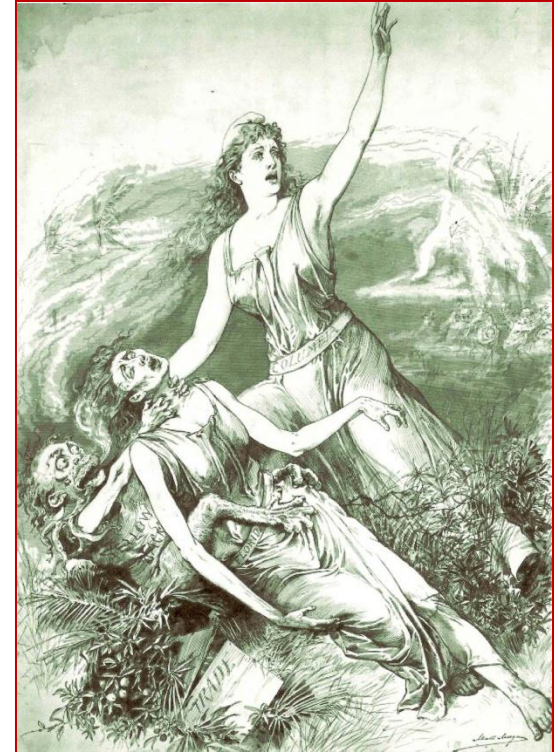
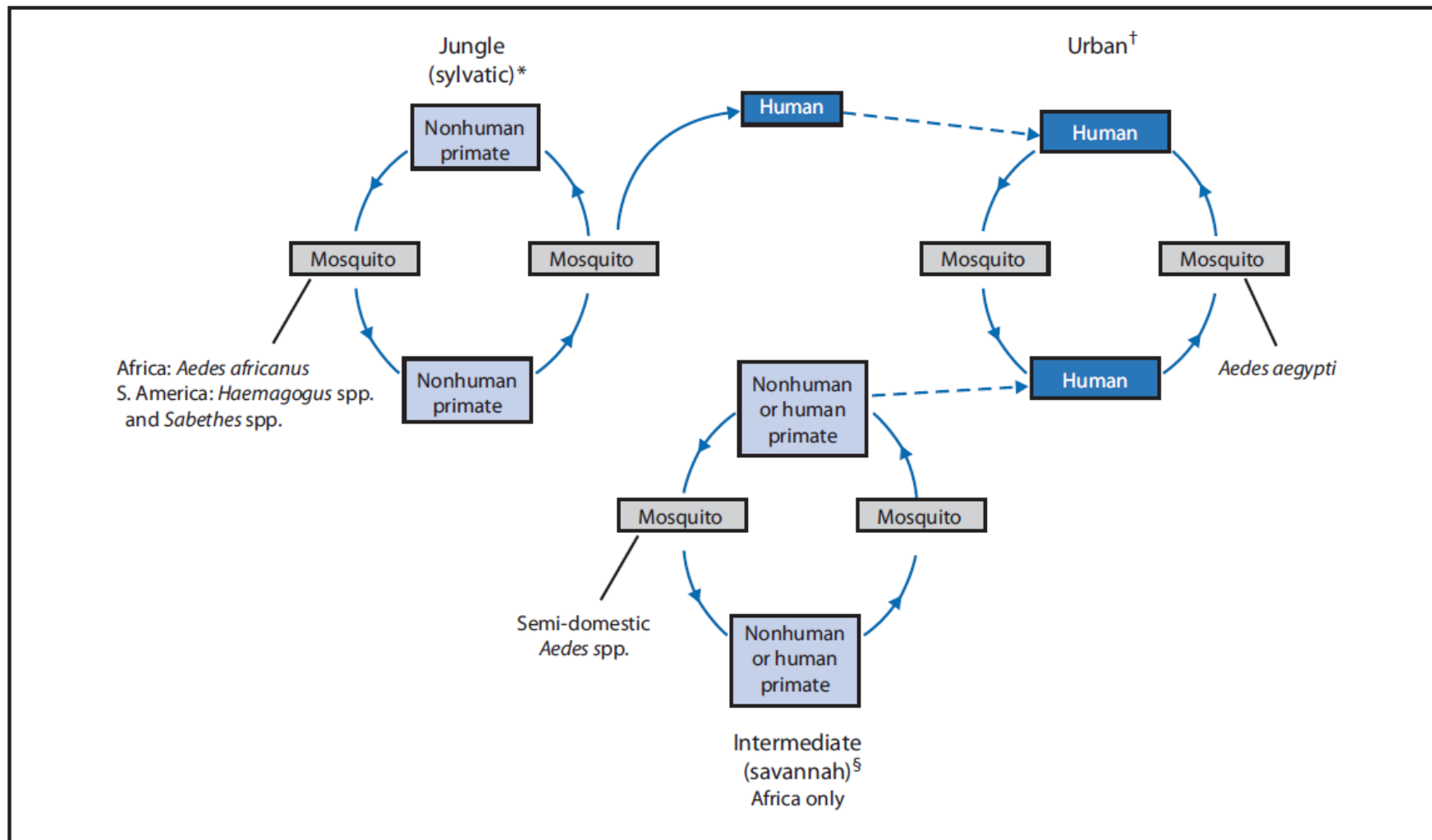


FIGURE 1. Transmission cycles for yellow fever virus



* The jungle (sylvatic) transmission cycle involves transmission of the virus between nonhuman primates and mosquito species found in the forest canopy. The virus is transmitted via mosquitoes from nonhuman primates to human when the humans encroach into the jungle during occupational or recreational activities.

† The urban transmission cycle involves transmission of the virus between human and urban mosquitoes, primarily *Ae. aegypti*. Viremic humans traveling from one region to another can feed into and serve as a source of infection for mosquitoes in other transmission cycles (dotted line).

§ In Africa, an intermediate (savannah) cycle involves transmission of YFV from tree hole-breeding *Aedes* spp. to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from nonhuman primate to humans or from human to human via these mosquitoes.



Yellow Fever Risk Map



Figure 3: Areas with risk of yellow fever virus transmission in South America, 2010

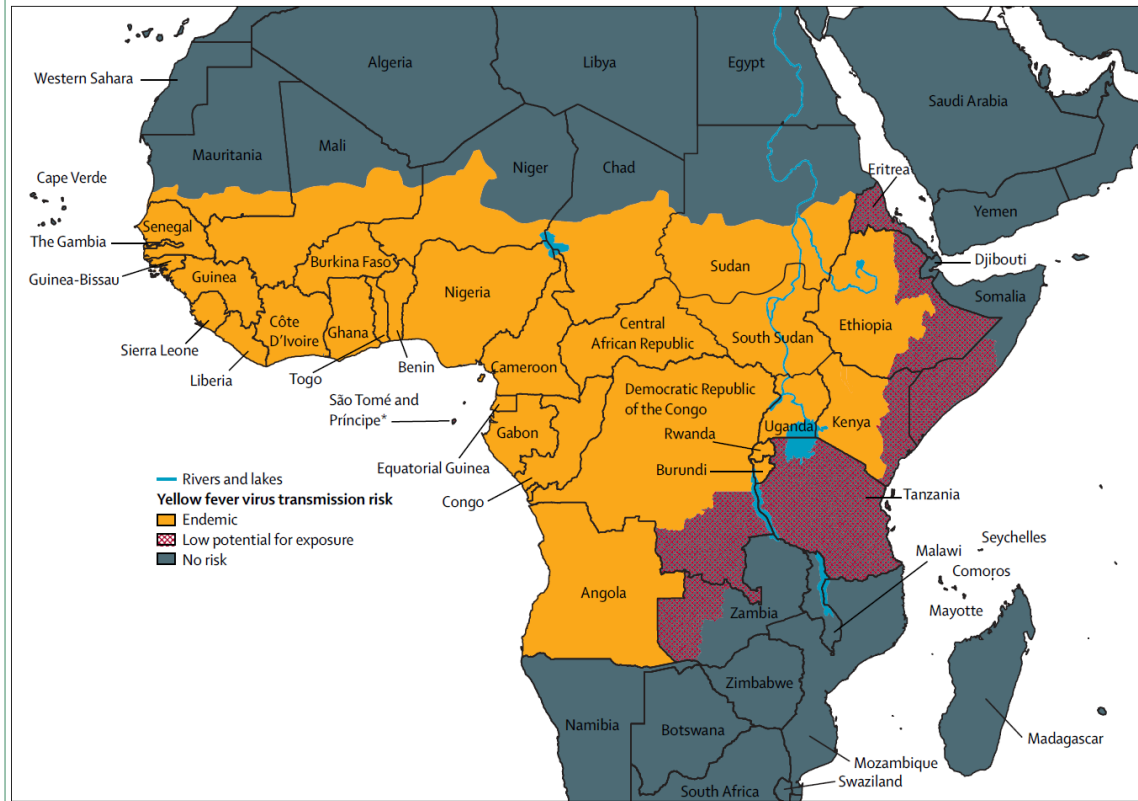


Figure 4: Areas with risk of yellow fever virus transmission in Africa, 2010

*São Tomé and Príncipe was classified as low potential for exposure.

Map is from the following publication: Jentes ES, Pomeroy G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. *Lancet Infect Dis.* 2011;11:622-32.



Disease Time-course

- Incubation period: 3-6 days
- Symptoms for ~ 3 days (viremia)
- Defervescence and short term improvement (remission)
- Fever and symptoms return (intoxication)
- Improvement (convalescence)



Figure 5. Yellow fever patient during the period of infection. The patient is febrile and acutely ill, with prominent conjunctival congestion. During this pre-icteric phase, the illness is difficult to differentiate from many other infectious diseases. Virus is present in the blood and the patient is infectious for blood-feeding mosquitoes.

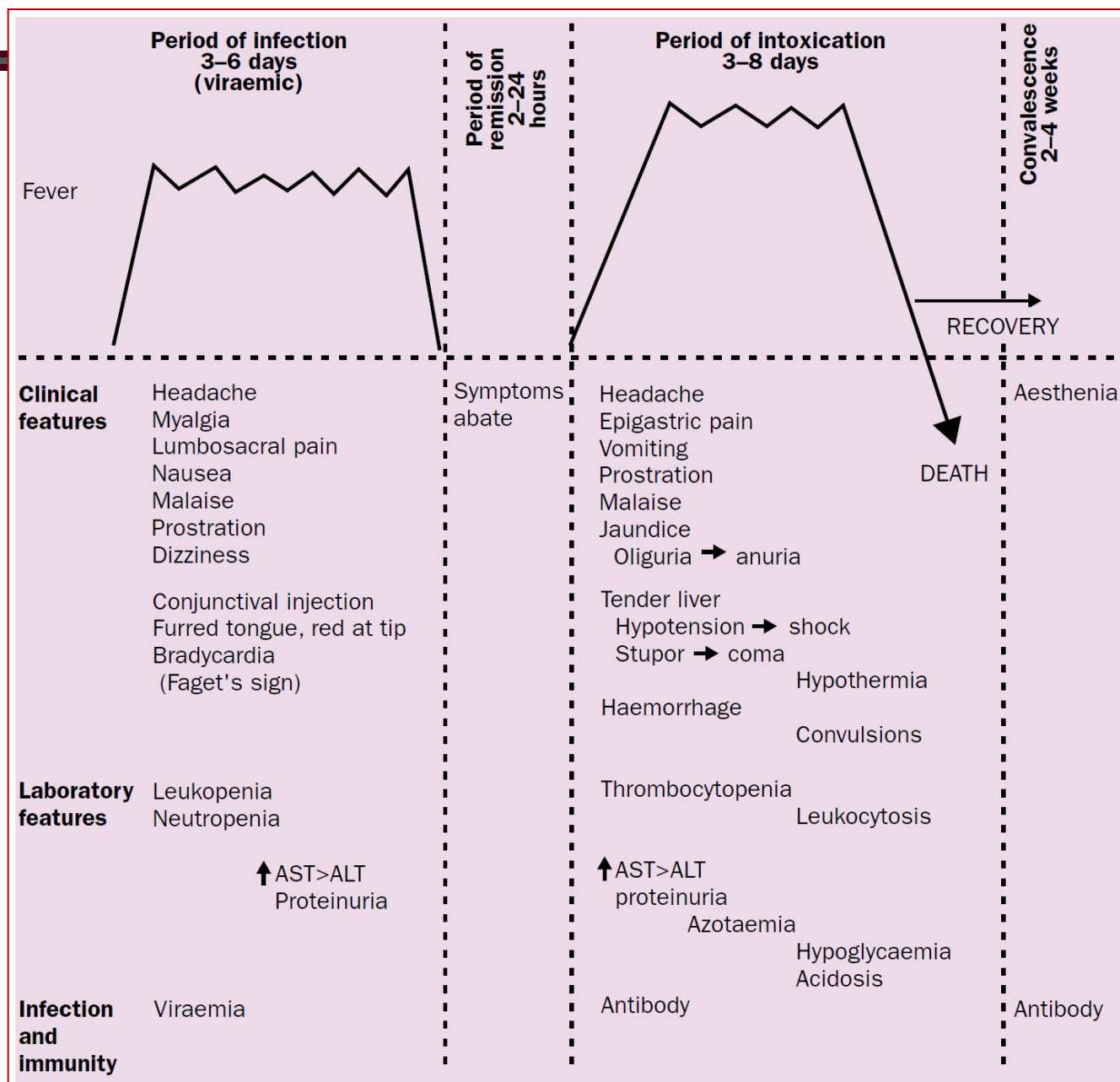


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

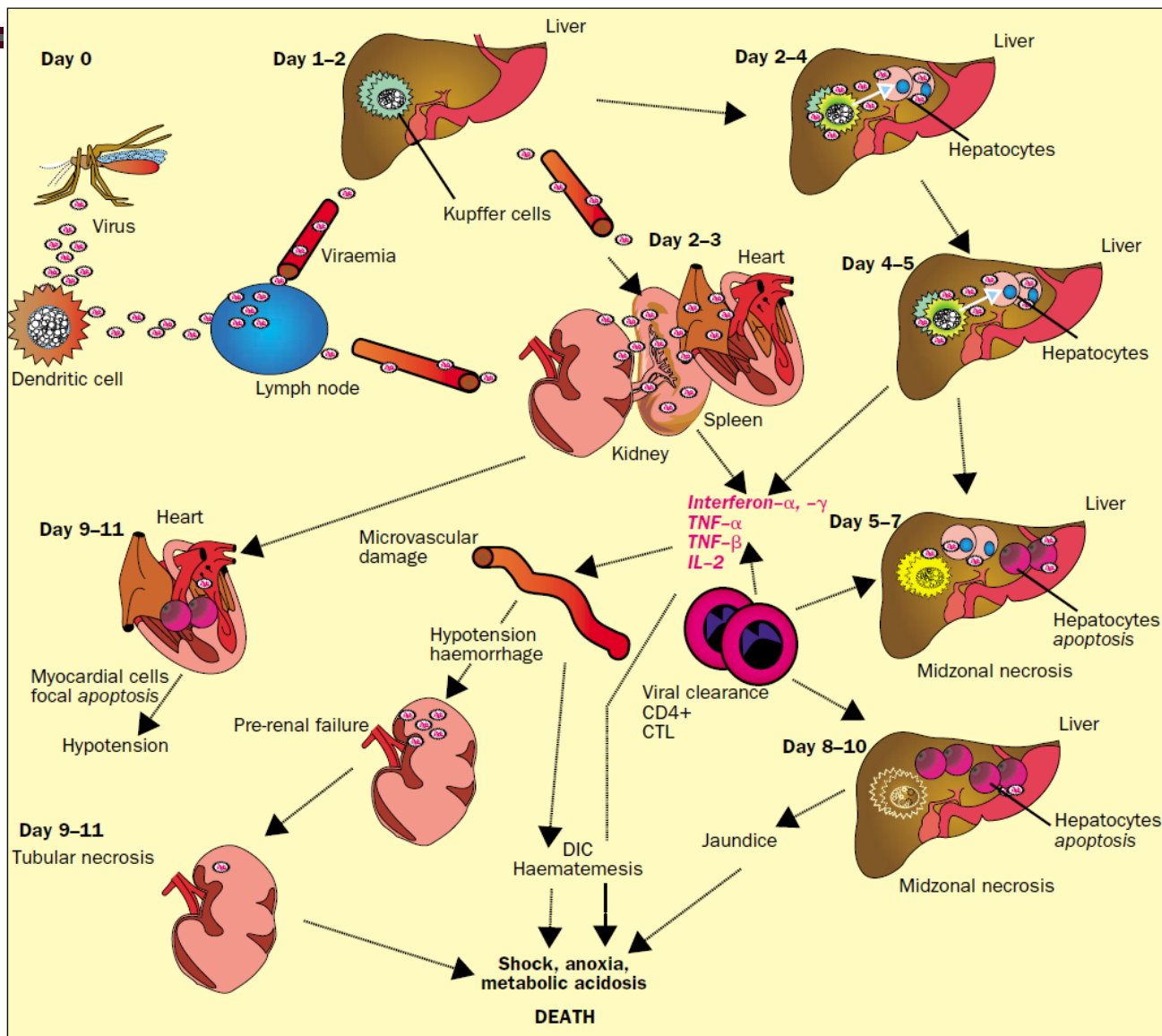


Figure 6. Pathogenesis of yellow fever based on studies in experimentally infected monkeys and human case reports (**bold**). Speculative mechanisms shown in *italics* are drawn from in-vitro data or reports on other flavivirus infections. CTL=cytotoxic T lymphocyte, DIC=disseminated intravascular coagulation, IL=interleukin.

Diagnosis

- Clinical Diagnosis
 - h/o travel to endemic area within the incubation period
- Advanced Diagnostics:
 - Virus Isolation (culture)
 - Rapid Diagnostics
 - PCR
 - Remember the window period
 - Antibody or Antigen detection (ELISA)
 - IgM for acute phase, coupled with convalescent antibodies (IgM/IgG)
 - Neutralization Ab are more specific for YF



Treatment Overview

- Supportive Care -- no specific therapy
 - Maintain nutrition and prevent hypoglycemia
 - NG tube to prevent gastric distention
 - Treatment of hypotension (IVF, pressors)
 - Supplemental oxygen
 - Correction of bleeding abnormalities
 - Dialysis
 - Treatment of secondary infections
 - Treatment of DIC

Certain medications should be avoided, such as aspirin or other non-steroidal anti-inflammatory drugs (such as ibuprofen and naproxen), because these may increase the risk for bleeding.

– PROTECT FROM FURTHER MOSQUITO EXPOSURE



Yellow Fever Vaccine 17D

- Has remained in continuous use since 1936
 - Over 400 million doses given
 - Protects 90%/10 days, 99%/30 days
- Long-lasting immunity
 - Countries may require boosting every 10 years
 - Studies have shown neutralizing Ab decades after dose
 - 81% of US WWII veterans with Ab after > 30yrs



1. WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fever.
2. Poland JD, Calisher CH, Monath TP. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ 1981;59:895-900.



Table 1. Yellow fever vaccine contraindications and precautions.

Contraindications

Age, <6 months

Thymus disease or history of thymus disease

Immunosuppression

Precautions

Age, 6–12 months

Age, ≥ 60 years for first-time vaccinees

Pregnancy

Lactation

Asymptomatic HIV infection with laboratory verification of adequate immune system function

Hypersensitivity to eggs

Hypersensitivity to gelatin

Family history of adverse events associated with yellow fever vaccine



Yellow Fever Vaccine Reactions

- Common
 - Fever, Headache, body aches 5-10 days
 - Injection site inflammation 1-5 days
- Severe
 - Hypersensitivity reactions (including anaphylaxis)
 - YF vaccine-associated neurologic disease (YEL-AND)
 - YF vaccine-associated viscerotropic disease (YEL-AVD)



Yellow Fever Vaccine Reactions

Viscerotropic (hepatotropic) infection:

- transient viremia
- damage to liver, spleen, kidneys and heart
- hemorrhage
- in nature, occurs only in humans and non-human primates
- molecular mechanisms of infection type are poorly understood

Neurotropic infection:

- infects brain parenchyma and causes encephalitis
- in nature, occurs in susceptible rodents
- in “nature” wild-type viruses do not result in neurotropic disease
- can occur in primates when vaccine strain “reverts” to virulent phenotype→ Vaccine Associated Neurotropic Disease

Current Opinion in Immunology



Yellow Fever Vaccine Reactions

YEL-AND

- primary vaccinees
- 2 to 30 days post-vaccination
- fever ($>101.5^{\circ}\text{F}$ $> 24\text{h}$) and headache ($>24\text{h}$ duration)
- focal neurological dysfunction (aphasia, paresis, etc)
- mental status change
- new-onset seizure or recurrence
- CSF pleocytosis ($> 5 \text{ WBC}/\text{mm}^3$) or elevated protein (>1.5 times normal)
- three distinct clinical entities
 - neurotropic disease
 - auto-immune CNS disease
 - auto-immune PNS disease
- recovery in 95% (CFR $<5\%$)

YEL-AVD

- primary vaccinees
- 2 to 5 days post yellow fever vaccination
- fever, myalgia and arthralgia
- elevated liver enzymes and bilirubin, sometimes progressing to liver failure
- thrombocytopenia, lymphocytopenia
- rhabdomyolysis
- hypotension, requiring vasopressors
- renal failure, requiring dialysis
- respiratory failure, requiring intubation
- recovery in 40% (CFR $> 60\%$), with higher CRF in women

Current Opinion in Immunology



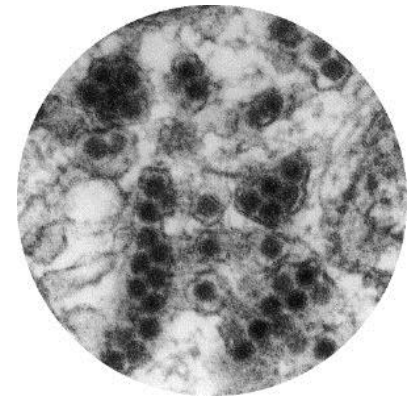
Question

- A 43 yo male is traveling on business throughout Southeast Asia. He will be traveling for 3 weeks (August) staying in hotels located in major urban centers. Tourist activities are planned in rural areas in Northern Thailand, Viet Nam and Cambodia. Activities will include elephant treks, river rafting, and camping. A previous trip to the same region was abruptly cancelled 4 years ago. He recalls receiving 1 dose of a vaccine to prevent a “brain infection.” He has no medical history. He has received all routine childhood vaccinations without adverse events. He has taken doxycycline for malaria prophylaxis in the past without adverse events.
- What is your guidance to the patient regarding Japanese encephalitis?
 - 1.Nothing, he is going to non-endemic areas during a low risk period.
 - 2.JE risk is high where he is travelling and during the period he is travelling, he should ensure use of personal protective measures (PPMs).
 - 3.JE risk is high, he should receive the final 2 doses of the JE vaccine series he started 4 years ago.
 - 4.JE risk is high, he should receive a new, complete series of JE vaccine and use PPMs during his trip.



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JE Virus

Japanese Encephalitis

- Most common viral encephalitis etiology worldwide
 - 160,000 reported cases 1966
 - 16,000 reported cases 1996
 - Impact of vaccination programs in endemic regions
 - Impact of development, esp Japan, Taiwan, ROK
 - Annual estimate is $\geq 50K$ cases
 - 2.5 cases/10,000 population at risk
- Primarily a disease of children
 - Naïve adults at similar risk (i.e., travelers, military)
- Most infections are subclinical/self-limited
 - Clinical cases have high mortality, morbidity
 - CFR ~25 -30%
 - Long-term disability 45 - 50%



Clinical Findings

- Incubation period 4 – 14 days
 - Sudden onset fever, chills and aches
 - Lethargy, HA, meningismus, N/V
 - Acute Flaccid Paralysis
 - Rapid onset paralysis despite normal consciousness
 - Weakness legs > arms, asymmetric
 - Flaccid paralysis also occurs in 5%-20% of comatose patients with "classic" JE
- Course
 - Occasionally fulminant
 - Short prodrome, deep coma, respiratory depression, posturing, death
 - Usually, improvement over ~ 1 week
 - Neuropsychiatric sequelae (years or is permanent)

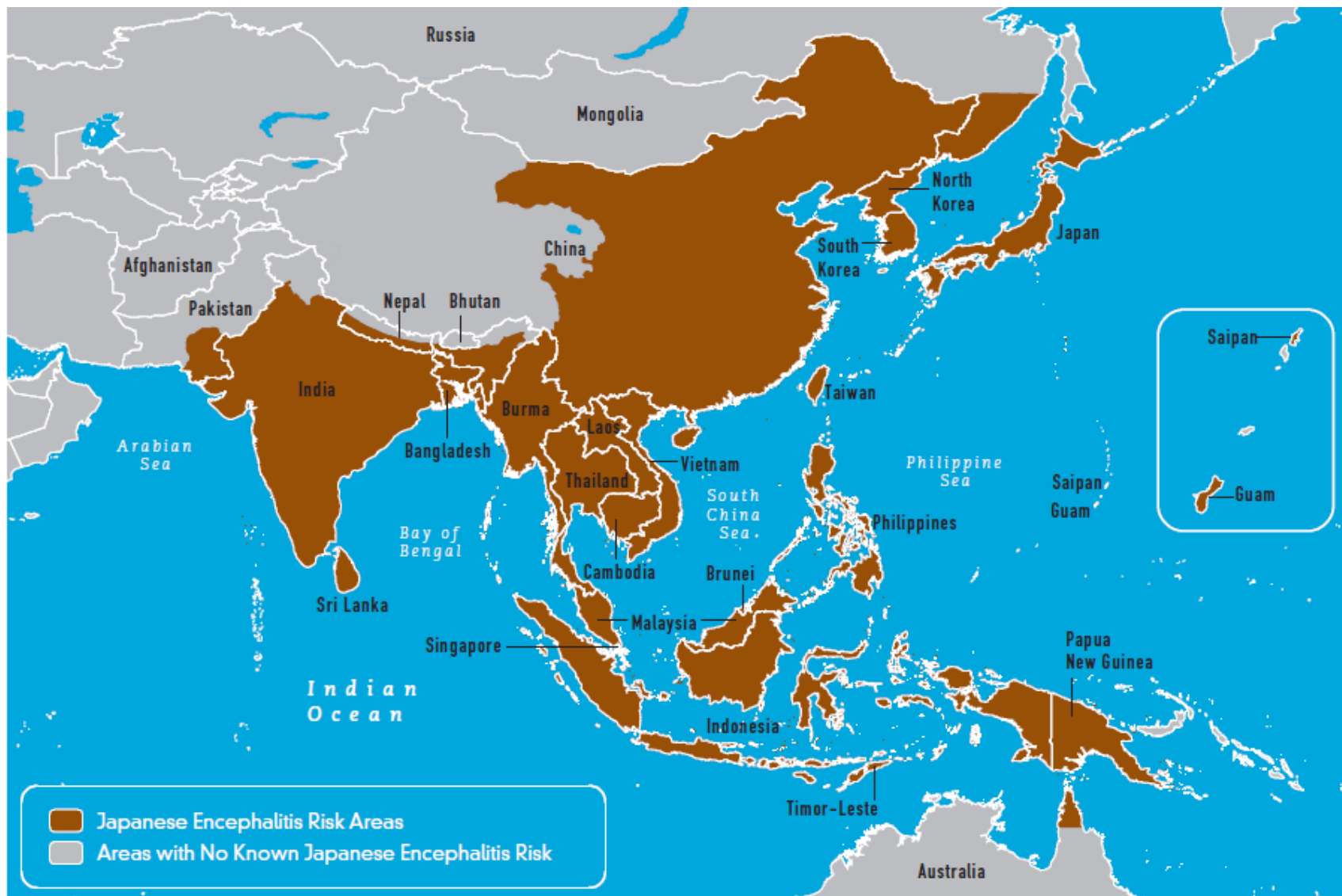


Transmission

- Vector: *Culex* mosquitoes
 - *Culex tritaeniorhynchus*
 - Breeds in marshes, rice paddies
 - Night-biting
- Zoonotic amplification
 - Domestic pigs
 - Migratory waterfowl
- Seasonal/climate factors
 - Summertime / post-rainy season
 - Increased vector number
 - Increased feeding behaviors
 - Increased viral replication



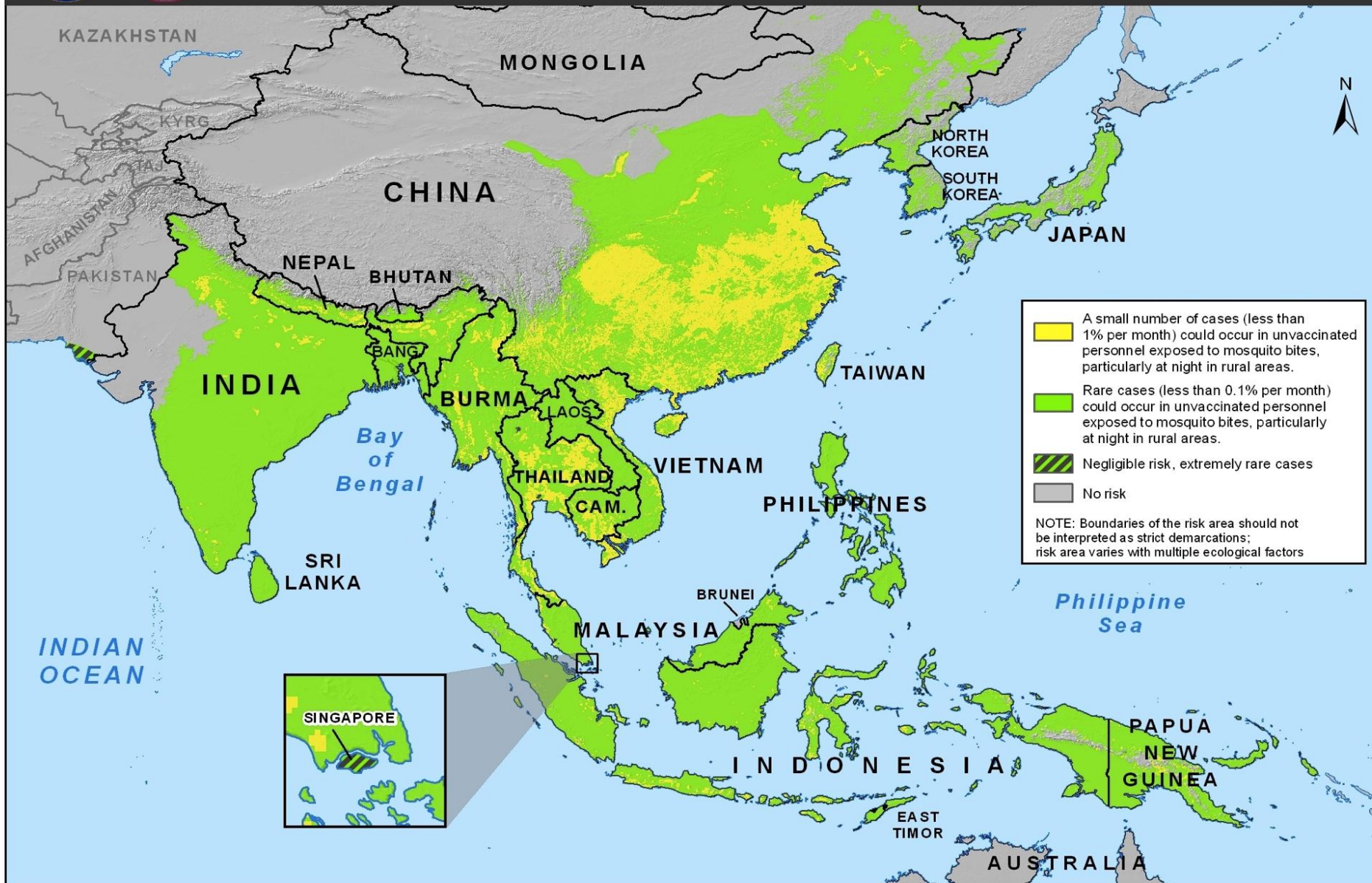
Japanese Encephalitis





PACOM: Japanese Encephalitis Risk to U.S. Forces

UNCLASSIFIED

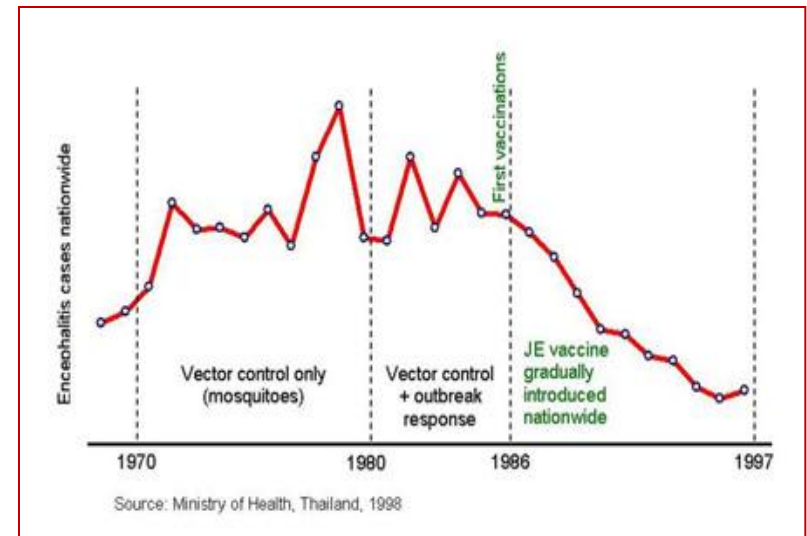


UNCLASSIFIED

22 May 2013 • DIA-NCMI

Prevention

- Vector control – difficult in endemic regions
 - Impractical, historically ineffective
 - Twilight-biting, marsh-breeding mosquitoes
- Reservoir control – difficult in endemic regions
 - Swine
 - Segregation impractical
 - vaccination expensive
- Vaccination
 - Mass pediatric vaccinations
 - Apparently highly effective



New JE Vaccines

- Live, attenuated SA 14-14-2 vaccine
 - Produced and used successfully in China for > 20 years
- Inactivated vero-cell derived JEV (Biken, Kaketsuken)
 - Inactivated Beijing JEV grown on Vero cells
- ChimeriVax-JE vaccine (Acambis/sanofi pasteur)
 - Live, recombinant vaccine (based on Yellow Fever 17D)
- Ixiaro (Intercell/Novartis/Biological E)
 - Inactivated vaccine
 - Derived from SA-14-14-2 JEV cultured in Vero cells
 - 2 doses at day 0 and day 28
 - Licensed in US for adult use 2009
 - US licensure for pediatric use, May 2013



Manufacturer's FDA-approved labeling

- INDICATIONS AND USAGE
 - Indicated for active immunization for the prevention of disease caused by JEV in persons 17 years of age and older.
- DOSAGE AND ADMINISTRATION
 - 2 doses administered 28 days apart.
 - Each 0.5mL dose is administered intramuscularly
 - Series should be completed at least 1 week prior to exposure
- CONTRAINDICATIONS
 - Severe allergic reaction(e.g., anaphylaxis) after a previous dose of IXIARO is a contraindication to administration of IXIARO.
- WARNINGS AND PRECAUTIONS
 - IXIARO contains protamine sulfate, a compound known to cause hypersensitivity reactions in some individuals.



A Single Dose of Vero Cell–Derived Japanese Encephalitis (JE) Vaccine (Ixiaro) Effectively Boosts Immunity in Travelers Primed With Mouse Brain–Derived JE Vaccines

Erra, et al. Clin Infect Dis. 2012 September 15; 55(6): 825–834.

	Response Rate After 1 Dose of JE-VC ^a		Protection Rate After 1 Dose of JE-VC ^b		Geometric Mean Titers After 1 Dose of JE-VC ^b	
	Nonprimed	Primed	Nonprimed	Primed	Nonprimed	Primed
PRNT Nakayama	39% (10/26)	98% (41/42)	40% (10/25)	100% (17/17)	<10	236
PRNT SA14-14-2	42% (11/26)	95% (40/42)	40% (10/25)	100% (17/17)	12	236

Table 4

Subgroup Analysis of Response Rates, Protection Rates, and Geometric Mean Titers After a Single Dose of Vero Cell–Derived Japanese Encephalitis Vaccine in Previously Primed (Group MB-VC) and Nonprimed (Group VC) Travelers



**IXIARO (Japanese Encephalitis Vaccine, Inactivated,
Adsorbed)
Suspension for Intramuscular Injection
Initial U.S. Approval: 2009**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IXIARO is a vaccine indicated for the prevention of disease caused by Japanese encephalitis virus (JEV). IXIARO is approved for use in individuals 2 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration only.

2.1 Dosage and Schedule

Primary Series:

Children 2 months to <3 years of age: Primary immunization with IXIARO consists of two (2) 0.25 mL doses, administered 28 days apart.

Individuals 3 years of age and older: Primary immunization with IXIARO consists of two (2) 0.5 mL doses, administered 28 days apart.

Complete the primary immunization series at least 1 week prior to potential exposure to JEV.

Booster Dose:

Individuals 17 years of age and older: If the primary series of two doses was completed more than 1 year previously, a booster dose may be given if ongoing exposure or re-exposure to JEV is expected.

Infants, children and adolescents 2 months to <17 years of age: The safety and immunogenicity of a booster dose has not been evaluated.



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

MAY 07 2013

“Risk determination, therefore, must take into account human activities and the proximity of high-risk areas rather than broad geographic risk determinations. The following guidelines should be used for administration of the JE vaccine:

- 1. Individuals deploying to areas in Pacific Command (PACOM) should be administered the JE vaccine in accordance with the latest PACOM Force Health Protection Guidance.**
- 2. We advise and highly recommend JE vaccine for Service members, Department of Defense civilians, and beneficiaries who are, or will be, stationed or visiting for more than 30 days in endemic areas. This includes those who would be based in urban areas, but likely to visit endemic rural or agricultural areas during a high-risk period of JE transmission. Administer booster dose after 1 year according to the ACIP recommendations if risk of exposure continues. Timing of additional booster doses has not yet been determined.”**



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“3. We advise recommendation of JE vaccine for the following Service members and beneficiaries:

- Short-term (<1 month) travelers to endemic areas during the JE transmission season if they plan to travel outside of an urban area and have an increased risk for JE exposure.
 1. spending substantial time outdoors in rural or agricultural areas, especially during the evening or night;
 2. participating in extensive outdoor activities (e.g., camping, hiking, trekking, biking, fishing, hunting, or farming); and
 3. staying in accommodations without A/C, screens, bed nets.
- Travelers to an area with an ongoing JE outbreak;
- Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel; and
- Laboratory workers with potential exposure to infectious JE virus.”



Question

- A 52-year-old female had malaise and rash after a 9-day business trip to Jakarta, Indonesia; she is an ex-pat living in Australia. Symptoms included fatigue and non-specific malaise, followed by headache. On day 4, a maculopapular rash developed (trunk, back, and limbs). The rash was accompanied by generalized myalgia, some loose bowel movements, and an occasional dry cough. She did not develop sweats or rigors. Examination on day 5 showed mild bilateral conjunctivitis, rash, but no lymphadenopathy or tenosynovitis. You treat her symptoms. During a follow up visit on day 7 she reports her husband has become ill with a similar syndrome.
- What is your leading differential diagnosis?
 - A. Dengue
 - B. Chikungunya
 - C. Ross River
 - D. Zika virus
 - E. Leptospirosis



Arboviruses

- Family Flaviviridae
 - Genus Flavivirus (53 species, examples below)
 - Dengue, Japanese encephalitis, Kyasanur Forest disease, MVE, Omsk hemorrhagic fever, Powassan, Rio Bravo, SLE, TBE, WNV, Yellow fever, **Zika virus**
 - Genus Hepacivirus (1 species)
 - Hepatitis C virus
 - Genus Pegivirus (2 species)
 - Pegivirus A, Pegivirus B
 - Genus Pestivirus (4 species)
 - Border disease virus, Bovine viral diarrheal virus 1, Bovine diarrheal virus 2, Classical swine fever virus



Zika Virus

- Flavivirus (family Flaviviridae)
- Isolated in 1948 from a rhesus monkey
 - Zika forest, near Entebbe, Uganda
- Serologic evidence of human infection in Africa and Asia
- Transmitted to humans by infected mosquitoes
 - *Aedes africanus*, *luteocephalus*, *aegypti*, others
- Yap Island outbreak (2007) the first outside Asia, Africa
- Human to human transmission suspected



Zika Virus

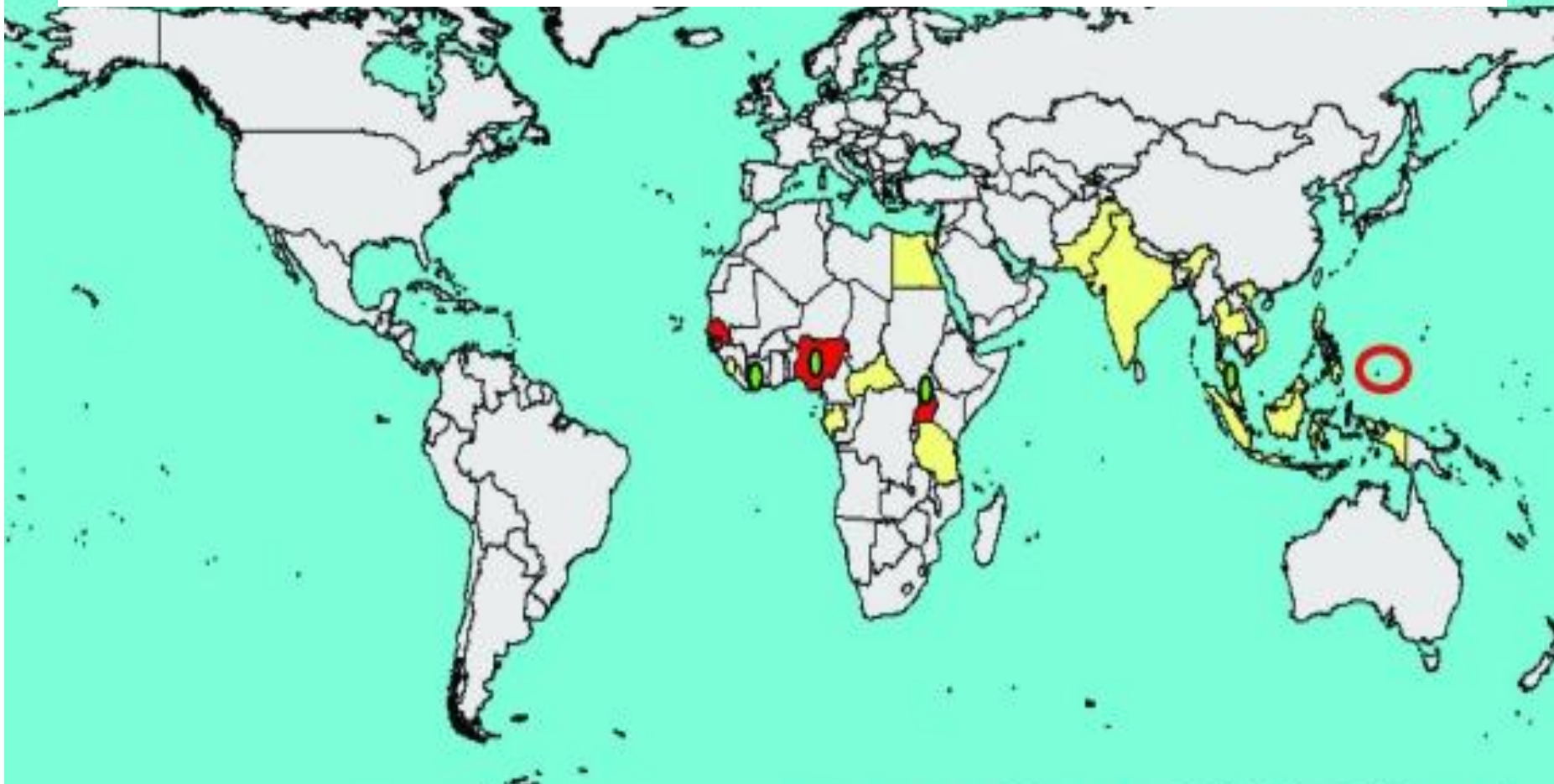


Figure 1 Approximate known distribution of Zika virus, 1947–2007. Red circle represents Yap Island. Yellow indicates human serologic evidence; red indicates virus isolated from humans; green represents mosquito isolates.

Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)

* Cases of measured and subjective fever are included.



Table. Reported or observed clinical signs and symptoms in persons with Zika virus infection, 1962–2010

Sign or symptom	Country, year of infection origin,* no. (%) patients					
	Uganda, 1962, n = 1	Laboratory acquired, 1973, n = 1	Indonesia, 1977–1978, n = 7	Micronesia, 2007, n = 28	Senegal/United States, 2009, n = 3	Cambodia, 2010, n = 1
Fever	1 (100)	1 (100)	7 (100)	20 (65)		1 (100)
Headache	1 (100)			14 (45)	3 (100)	1 (100)
Malaise	1 (100)		5 (71)		3 (100)	
Maculopapular rash	1 (100)			28 (100)	3 (100)	
Fatigue or myalgia	1 (100)	1 (100)	1 (14)	14 (45)	1 (33)	
Arthritis and arthralgia			1 (14)	20 (65)	3 (100)	
Chills		1 (100)	2 (29)		2 (67)	
Dizziness			5 (71)			
Joint swelling or edema				6 (19)	2 (67)	
Stomachache			6 (86)			
Retro-orbital pain		1 (100)		12 (39)		
Conjunctivitis			1 (14)	17 (55)	1 (33)	
Anorexia			4 (57)			
Photophobia					1 (33)	
Vomiting			1 (14)	3 (10)		
Diarrhea			3 (43)			
Constipation			3 (43)			
Sore throat						1 (100)
Cough						1 (100)
Aphthous ulcer					2 (67)	
Hypotension			2 (29)			
Hematuria			1 (14)			
Prostatitis					1 (33)	
Hemospermia					1 (33)	
Sweating		1 (100)				
Lightheadedness					1 (33)	

*References: Uganda (2), laboratory-acquired (10), Indonesia (5), Micronesia (9), Senegal/United States (4). Blank cells indicate no reported information.



Probable Non–Vector-borne Transmission of Zika Virus, Colorado, USA

Brian D. Foy, Kevin C. Kobylinski, Joy L. Chilson Foy, Bradley J. Blitvich, Amelia Travassos da Rosa, Andrew D. Haddow, Robert S. Lanciotti, and Robert B. Tesh



Figure. Maculopapular rash on patient 3 infected with Zika virus, Colorado, USA.

Zika Virus

- Diagnosis
 - Travel to known area of transmission
 - Compatible clinical syndrome
 - Serology (cross reactivity with dengue)
 - IgM ELISA
 - Neutralizing antibodies
 - Molecular
 - RT-PCR
 - Sequencing



Zika Virus

- Prevention
 - No vaccine or prophylactic drug
 - PPMs and vector avoidance
- Treatment
 - Supportive
 - Close resemblance to dengue on presentation likely warrants avoidance of NSAIDS and aspirin until Dx
 - Case report of possible human to human transmission requires counseling



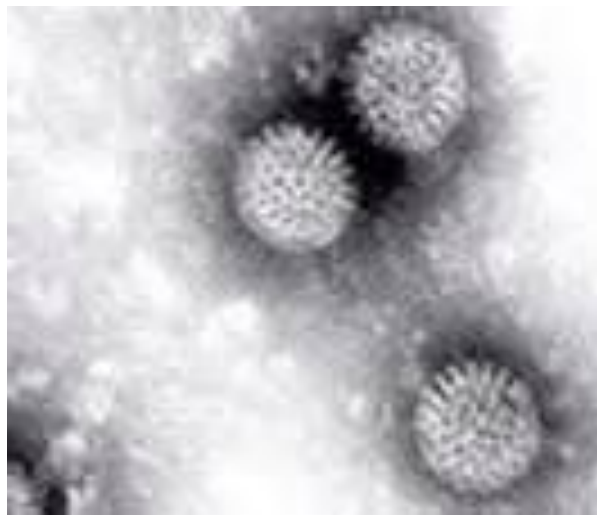
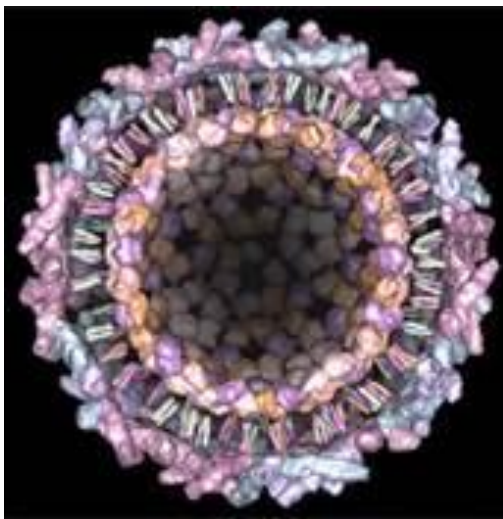
Question

- 32 yo WM presents with complaints of joint pain and severe fatigue 5 days after returning from a vacation in Northeastern Australia. Although he slept indoors, tourist activities were predominantly outdoors. He had no fresh water exposure. Food and beverages were prepared by the hotel and tourism company. He had no animal exposures. He is ill appearing and uncomfortable. VS, including temperature, are normal. On exam he has symmetrical tenderness and warmth in his ankle and knee joints, there is a L knee effusion. He has a faint macularpapular, non-pruritic rash on his trunk.
- What infection would be #1 on your differential diagnosis?
 - A. Leptospirosis
 - B. Malaria
 - C. Chikungunya
 - D. Dengue
 - E. Ross River virus



Arboviruses

- Family Togaviridae
 - Genus Alphavirus (30 species, examples below)
 - Barmah Forest, Chikungunya, EEE, O'nyong-nyong, **Ross River**, Sinbis, VEE, WEE
 - Genus Rubivirus (1 species)
 - Rubella



Ross River Virus

- Mosquito-transmitted *Alphavirus* (*Aedes* spp.)
- Endemic /enzootic in Australia and Papua New Guinea
- Most common arboviral disease in Australia
 - Thousands of cases annually (avg. 4,745; 1991-2000)
- Classic syndrome
 - Constitutional symptoms, rash, rheumatic manifestations

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2001, p. 909–932
0893-8512/01/\$04.00+0 DOI: 10.1128/CMR.14.4.909–932.2001
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Ross River Virus Transmission, Infection, and Disease: a Cross-Disciplinary Review

DAVID HARLEY,^{1,2} ADRIAN SLEIGH,^{1*} AND SCOTT RITCHIE²

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2001, p. 909–932

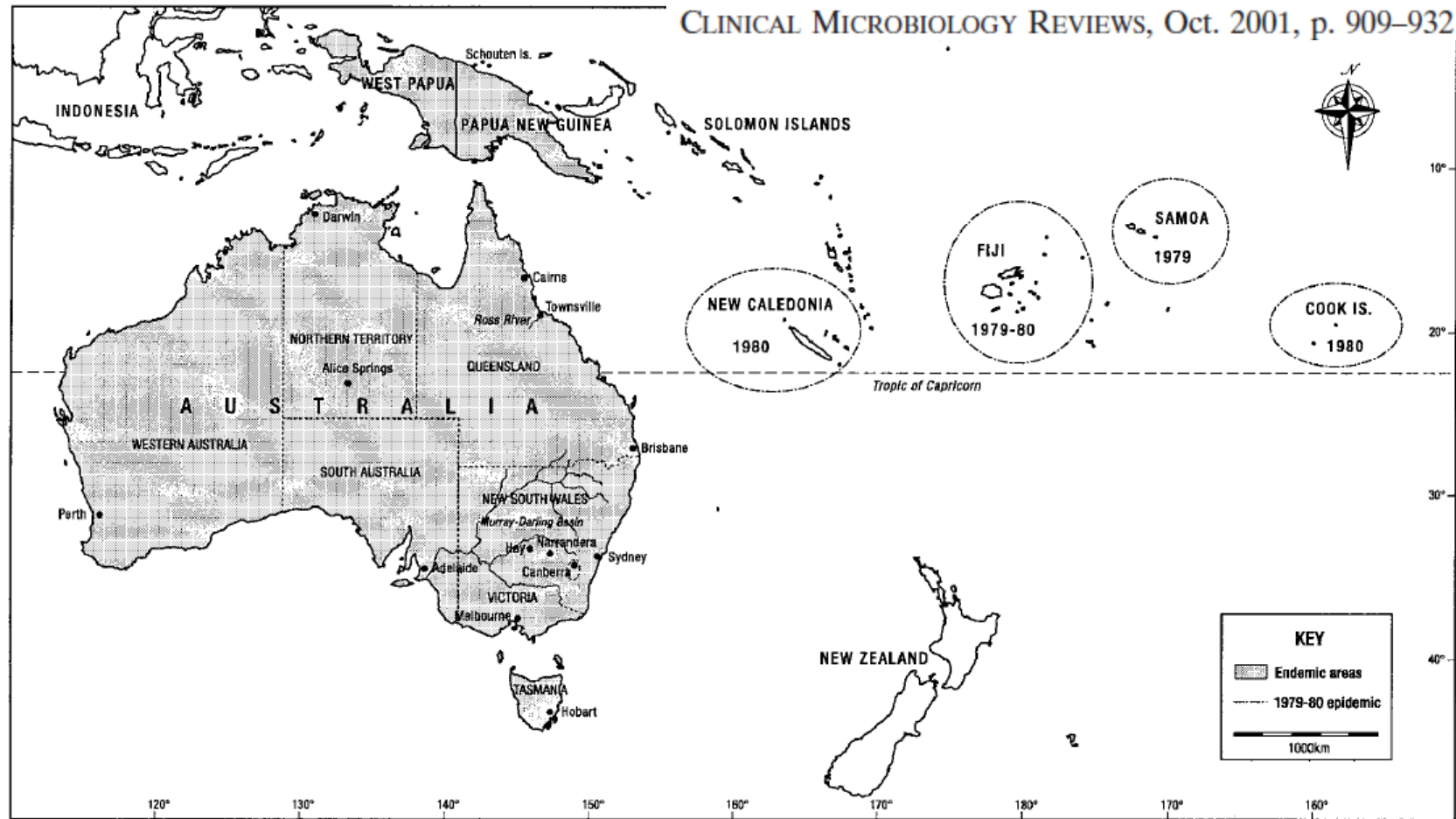


FIG. 1. Map showing cities, towns, and geographical features discussed in the text, areas where RRV is endemic, and the 1979 to 1980 South Pacific epidemic of RRV disease.



Legend
Rate per 100 000 population

0.5-11.0
11.1-22.7
22.8-40.5
40.6-192.4
92.5-242.6

Ross River Virus Clinical Manifestations

- RRV incubation period ~7 to 9 days
- Asymptomatic infections in ~30%
- Symptoms may last for months or longer (co-morbidities)
- Constitutional symptomatology
 - Fever (1/3 to 1/2 of patients)
 - Rash, fever, and arthralgia may occur in any sequence
 - Fatigue typically affects over 50% of patients
 - Myalgia is common
 - Lymphadenopathy occurs quite often
 - Sore throat and coryza less frequently
 - Diarrhea is rare



• Joint manifestations

- Symmetrical and acute in onset
- Tenderness with minor restriction of movement
- May have extreme redness and swelling
- Effusions are common
- Peripheral joints are predominantly involved
- Ankles, fingers, wrists, and knees commonly affected

<http://www.bing.com/images/search?q=Ross+river+virus&Form=R5FD0#view=detail&id=2AC4DDD2BF5E090FC561D2C0F252A08D93D7BE63&selectedIndex=32>

Accessed 9 SEP 2013



• Rash

- Usually lasts 5 to 10 days
- May be the sole manifestation of infection
- Appears mainly on the limbs and trunk
- Maculopapular, vesicular, or purpuric

Reprinted from AUSTRALIAN FAMILY PHYSICIAN Vol. 38, No. 8, August 2009

Table 2. Frequency of symptoms and signs of Ross River virus^{20–23}

Symptoms/sign	Frequency (%)
Joint pains	95
Tiredness	90
Fever	50–60
Myalgia	60
Rash	40–60
Headache	50
Joint swelling	50
Depression	45



Ross River Virus Transmission, Infection, and Disease: a Cross-Disciplinary Review

DAVID HARLEY,^{1,2} ADRIAN SLEIGH,^{1*} AND SCOTT RITCHIE²

TABLE 1. Joints affected by RRV disease

Joint	Frequency of joint involvement (% of cases)				
	Seglenieks and Moore (180) (n = 115)	Aaskov et al. ^a (4) (n = 36)	Mudge and Aaskov (144) (n = 400)	Condon and Rouse (33) (n = 189)	Westley-wise et al. (218) (n = 80)
Fingers		50 ^c	80	81	63
Hand	45				
Thumb			53	58	
Wrist	36	70	80	100	61
Elbow	17	40	44	71	
Shoulder		38	47	62	
Hip	4	10	27		
Knee	39	80	80	100	64
Ankle	50	78	88	97	64
Feet	49	36			
Toes			47		
Back	14 ^b	36	37	56	
Neck		36	12	70	
Jaw			10	15	

^a Percentages taken from a bar graph.

^b Includes back or neck.

^c Includes fingers and hand.



- Diagnosis
 - Serology
 - Acute and convalescent samples (14 days apart)
 - Demonstrate 4 fold rise in IgG antibody
 - Neutralizing antibodies by PRNT
 - Identify peripheral RNAemia (?)
- Treatment
 - No known treatment which alters disease course
 - Treat symptoms
 - NSAIDS
 - Physical therapy, hydrotherapy, etc.
 - Reassurance



Arboviruses

- Family Bunyaviridae
 - Genus Nairovirus
 - Crimean–Congo hemorrhagic fever virus (CCHF)
 - Genus Orthobunyavirus
 - California encephalitis virus
 - La Crosse encephalitis virus (LACV)
 - Bunyamwera virus
 - Genus Phlebovirus
 - Rift Valley fever virus (RVFV)
 - Toscana virus (TOSV)



Arboviruses

- Family Reoviridae
 - Subfamily Sedoreovirinae
 - Genus Orbivirus
 - African horse sickness virus (AHSV)
 - Bluetongue disease virus (BTV)
 - Equine encephalosis virus (EEV)
 - Genus Seadornavirus
 - Banna virus (BAV)
 - Subfamily Spinareovirinae
 - Genus Coltivirus
 - Colorado tick fever virus (CTFV)



Arboviruses

- Family Picornaviridae
 - Genus Parechovirus
 - Sebokele virus 1



Summary

- Arboviral diseases are pervasive and difficult to prevent
- Clinical syndromes overlap across viruses
 - RRV: constitutional symptoms, rash, joints
 - CHIK: constitutional symptoms, joint / tendon, chronic
 - ZIKA: constitutional symptoms, rash, conjunctivitis
 - JE: vaccine preventable disease, high morbid/mortality
 - YF: vaccine preventable, potential for severe Aes
 - DEN: most important arbovirus see other lecture
- Prevention and treatment
 - Know geographic distribution, PMMs, vaccinate (JE/YF)
 - Symptomatic treatment, avoid platelet modifying drugs



Questions?

